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Clinical features of Malaysian children hospitalized with community-acquired seasonal influenza

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SUMMARY

Objectives: The clinical impact of seasonal influenza is understudied in tropical countries. The aim of this study was to describe the clinical features and seasonal pattern of influenza in children hospitalized in Malaysia, and to identify predictors of severe disease.**Methods:** Children hospitalized with community-acquired, laboratory-confirmed influenza at a teaching hospital in Kuala Lumpur, Malaysia during 2002–2007 were identified retrospectively. Clinical data were collected, and predictors of severe disease were identified by multivariate logistic regression. All influenza cases from 1982 to 2007 were also analyzed for seasonal patterns.**Results:** A total of 132 children were included in the study, 48 (36.4%) of whom had underlying medical conditions. The mean age was 2.5 years and 116 (87.9%) were <5 years old. The most common presenting features were fever or history of fever, cough, rhinitis, vomiting, and pharyngitis. Severe influenza was seen in 16 patients (12.1%; nine previously healthy), including 12 (9.1%; eight previously healthy) requiring intensive care. There were three (2.3%) deaths. Severe disease was associated with age <12 months, female sex, and absence of rhinitis on admission. Influenza was seen year-round, with peaks in November–January and May–July.**Conclusions:** Seasonal influenza has a considerable impact on children hospitalized in Malaysia, in both the healthy and those with underlying medical conditions.

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1. Introduction

Influenza is a major cause of respiratory infections worldwide, resulting in considerable morbidity and mortality. Children aged <5 years and those with underlying medical conditions are at particular risk.¹ Much of the data on pediatric influenza comes from developed countries in temperate climates, which have distinct seasonal peaks in winter.² Reported hospitalization rates have ranged from 0.9 to 3.2 per 1000 children aged <2 years.^{3–6} Vaccination of children against seasonal influenza is therefore widely recommended in temperate countries.^{7,8}

In contrast, much less is known about the clinical impact of childhood seasonal influenza in tropical countries, mainly due to a perception that influenza is not a significant health problem⁹ and to a lack of diagnostic virology facilities. However, studies from tropical Singapore¹⁰ and subtropical Hong Kong¹¹ have indicated

that the burden of influenza equals or even exceeds rates seen in temperate countries. With avian influenza (H5N1) and pandemic influenza A (H1N1) originating from developing countries, a detailed understanding of influenza becomes increasingly critical in these less well-studied areas.

This study aimed to describe the clinical features of children hospitalized with laboratory-confirmed seasonal influenza in tropical Malaysia. In particular, we focused on clinical presentations, complications, and predictors of severe disease. Influenza cases over a 25-year period were also examined for seasonal patterns.

2. Materials and methods

2.1. Study population

The University Malaya Medical Centre (UMMC) is a 900-bed teaching hospital in Kuala Lumpur, Malaysia. It has 130 pediatric beds and approximately 6000 pediatric admissions annually. All pediatric patients <15 years of age who were admitted with laboratory-confirmed influenza from 2002 to 2007, were identified

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using data from the diagnostic virology laboratory. Laboratory-confirmed influenza was defined as the detection of influenza virus antigen by immunofluorescence or isolation of influenza virus, from a clinical specimen. Nosocomial infections, defined as onset of influenza more than 48 h after admission, were excluded.

2.2. Study design

This study was approved by the hospital's medical ethics committee. The medical records of all identified cases were retrospectively reviewed, and data on demographics, clinical presentation, laboratory tests, treatment, and outcomes were collected using a standard form.

A patient was defined as having severe influenza disease in the event of death, admission to the pediatric intensive care unit (PICU), ventilation, or a serious influenza-associated complication present on admission, such as myocarditis, meningitis, or sepsis/hypotension requiring inotropic support. Severe bacterial super-infections due to organisms other than those usually associated with influenza (e.g., *Staphylococcus aureus* and *Streptococcus pneumoniae*) were considered to be co-existing with, rather than directly caused by, influenza. We identified underlying high-risk medical conditions that predispose to severe disease, as described by the Advisory Committee on Immunization Practices (ACIP).⁷

2.3. Virology

Nasopharyngeal aspirates were routinely screened for respiratory viruses including influenza A and B with the Respiratory Virus Panel direct immunofluorescence assay (Millipore, Billerica, USA). All respiratory specimens were inoculated into Madin Darby canine kidney (MDCK), Vero, and A549 cells, and monitored daily for cytopathic effect (CPE) for 14 days. Hemadsorption with human type O blood was performed on MDCK cells with no CPE to detect the presence of influenza virus. Direct immunofluorescence was used to confirm the identity of respiratory virus isolates.

2.4. Statistical analysis

Statistical analysis was carried out using SPSS 15.0 (SPSS Inc., Chicago, USA). Descriptive analysis was performed on the data. For univariate analysis, Mann–Whitney U-tests were used for continuous variables and Chi-square or Fisher's exact tests were used for categorical variables. A two-tailed *p*-value of <0.05 was considered significant. To determine predictors for severe disease, univariate logistic regression was carried out on selected variables. Odds ratios (OR) with 95% confidence intervals (CI) were calculated. Variables with a *p*-value of <0.25 were then considered in the multivariate regression model, using the likelihood ratio test. The resulting parsimonious model was tested for collinearity and interactions. To assess the final model, the Hosmer and Lemeshow goodness-of-fit test was performed, and the area under the curve of the receiver operating characteristic curve was calculated.

2.5. Seasonality

The dates of all specimens with laboratory-confirmed influenza from 1982 to 2007 were obtained from laboratory records. These included specimens from nosocomial cases and samples from external laboratories. Cases were aggregated for each calendar month, to minimize ascertainment bias due to improvements in awareness or laboratory techniques. The percentage of confirmed influenza cases over the number of specimens tested was also calculated, to minimize the effect of the varying numbers of samples received in the laboratory over the years.

3. Results

3.1. Patients

A total of 160 pediatric inpatients with laboratory-confirmed influenza were seen in 2002–2007, ranging from 19 to 32 patients yearly, or 0.2% to 0.6% of annual pediatric admissions (mean 0.3%). Of these, 25 (15.6%) had nosocomially acquired influenza, and the medical records for a further three (1.9%) were unavailable. The remaining 132 (82.5%) patients were included in the study. The mean age was 2.5 ± 2.9 years; 116 (87.9%) patients were <5 years old and 75 (56.8%) were <2 years old.

There were 48 (36.4%) children with ACIP-designated high-risk medical conditions, including asthma (*n* = 19), immunosuppression (*n* = 11), and chronic cardiovascular (*n* = 10), neurological or neuromuscular (*n* = 7), hepatic (*n* = 4) and other pulmonary (*n* = 3) disorders. Four children had more than one high-risk condition. Further demographic data are shown in Table 1.

3.2. Clinical data

The common presenting clinical features are shown in Table 2. Although fever was present in only 65 (49.2%) children on admission, 61 of the remaining 67 reported a prior history of fever. The mean duration of symptoms was 5.0 ± 4.3 days (median 4 days; range 1–21 days). The mean length of hospital stay was 6.2 ± 5.5 days (median 4 days; range 1–26 days), excluding one patient with a prolonged stay for social reasons. Antibiotics were given to 108 (81.8%) patients, most commonly amoxicillin–clavulanate (63 children). No antivirals were used.

Severe influenza was seen in 16 (12.1%) patients, nine of whom were previously healthy. These included 12 (9.1%) children admitted to the pediatric intensive care unit (PICU), eight of whom were previously healthy. All were transferred to the PICU directly or on the day following admission, except for one child who was transferred 19 days after admission with nosocomial pneumonia. The children admitted to the PICU had pneumonia (*n* = 8), sepsis (*n* = 2), *S. pneumoniae* meningitis (*n* = 1), and exacerbation of underlying heart failure (*n* = 1). A total of 12 children were ventilated.

Five children had co-existing bacteremia (non-typhoidal *Salmonella* species (*n* = 2), *Enterobacter* species (*n* = 1), and line-associated infections with *Streptococcus* (*n* = 1) and coagulase-negative *Staphylococcus* species (*n* = 1)). Three patients had co-existing bacterial gastroenteritis due to *Salmonella* species (*n* = 2) and *Campylobacter jejuni* (*n* = 1). There were five patients co-infected with other respiratory viruses, including respiratory syncytial virus (RSV), adenovirus, and parainfluenza virus. There were no differences in demographic and clinical features between patients infected with influenza A (*n* = 97, 73.5%) or B (*n* = 35, 26.5%).

There were three (2.3%) deaths. One was a 6-month old with no notable medical history, who had sepsis, multiorgan failure, and concurrent *Campylobacter* gastroenteritis.¹² The other two children, a 1-year-old with duodenal atresia and parenteral nutrition-associated cholestasis and a 4-year-old with relapsed acute leukemia, both died of pneumonia.

Compared to previously healthy patients, univariate analysis showed that the 48 patients with ACIP conditions were older (mean 3.3 vs. 2.1 years, *z* = −2.2, *p* = 0.026), had a shorter duration of symptoms (mean 3.5 vs. 5.9 days, *z* = −2.7, *p* = 0.006), were more likely to be given antibiotics (91.7% vs. 76.2%, Chi-square = 4.9, *p* = 0.034), and stayed in hospital for longer (mean 9.3 vs. 4.4 days, *z* = −5.8, *p* < 0.001). Patients with ACIP conditions were more likely to have severe influenza (14.6% vs. 10.7%), but this difference was not significant.

Table 1

Predictors of severe influenza disease in hospitalized children (N = 132)

| Predictor | n (%) | No. with severe influenza, n (%) | Crude OR (95% CI) | p-Value | Adjusted OR (95% CI) | p-Value |
|---|------------|----------------------------------|-------------------|---------|----------------------|-----------------|
| Age | | | | | | |
| <12 months | 43 (32.6) | 11 (25.6) | 5.78 (1.86–17.93) | 0.02 | 8.76 (2.31–33.14) | 0.01 |
| >12 months | 89 (67.4) | 5 (5.6) | 1.0 | | | |
| Sex | | | | | | |
| Male | 75 (56.8) | 6 (8) | 1.0 | | | |
| Female | 57 (43.2) | 10 (17.5) | 2.45 (0.83–7.19) | 0.10 | 3.69 (1.01–13.43) | 0.048 |
| Ethnicity | | | | | | |
| Malay | 97 (73.5) | 11 (11.3) | 1.0 | | | |
| Indian | 18 (13.6) | 0 | 0 | 1.00 | | |
| Chinese | 15 (11.4) | 4 (26.7) | 2.84 (0.77–10.49) | 0.12 | | NS ^c |
| Other ^a | 2 (1.5) | 1 (50) | – | – | | |
| ACIP condition | | | | | | |
| No | 84 (63.6) | 9 (10.7) | 1.0 | | | |
| Yes | 48 (36.4) | 7 (14.6) | 1.42 (0.49–4.10) | 0.51 | | |
| Duration of symptoms (days), mean | 5.0 | – | 0.84 (0.68–1.03) | 0.13 | | NS ^c |
| Clinical features on admission ^b | | | | | | |
| Rhinitis | | | | | | |
| No | 33 (25) | 10 (30.3) | 6.74 (2.22–20.46) | 0.001 | 8.66 (2.43–30.80) | 0.001 |
| Yes | 99 (75) | 6 (6.1) | 1.0 | | | |
| Cough | | | | | | |
| No | 12 (9.1) | 4 (33.3) | 4.50 (1.18–17.29) | 0.03 | | NS ^c |
| Yes | 120 (90.9) | 12 (10) | 1.0 | | | |
| Seizures | | | | | | |
| No | 117 (88.6) | 12 (10.3) | 1.0 | | | |
| Yes | 15 (11.4) | 4 (26.7) | 3.18 (0.88–11.57) | 0.08 | | NS ^c |
| Influenza diagnosis | | | | | | |
| Positive IF | 72 (54.5) | 9 (12.5) | 1.0 | | | |
| Virus culture only | 60 (45.5) | 7 (11.7) | 0.96 (0.33–2.75) | 0.94 | | |
| Influenza type | | | | | | |
| A | 97 (73.5) | 13 (13.4) | 1.0 | | | |
| B | 35 (26.5) | 3 (8.6) | 0.61 (0.16–2.27) | 0.46 | | |
| Respiratory virus co-infection | | | | | | |
| No | 127 (96.2) | 15 (11.8) | 1.0 | | | |
| Yes | 5 (3.8) | 1 (20) | 4.00 (0.67–23.86) | 0.13 | | NS ^c |

OR, odds ratio; CI, confidence interval; ACIP, Advisory Committee on Immunization Practices; ^a IF, immunofluorescence; NS, not significant.^a Not analyzed as heterogeneous (non-specific) group.^b Other clinical features not found to be associated with severe disease, and not shown in this table: fever, vomiting, sore throat, diarrhea, rash, and stridor.^c Tested in the multivariate analysis and found not to be significantly associated with severe disease.

3.3. Predictors of severe disease

The final multivariate regression model (Table 1) showed that severe disease was associated with age <12 months (OR 8.76, 95% CI 2.31–33.14), female sex (OR 3.69, 95% CI 1.01–13.43), and absence of rhinitis at presentation (OR 8.66, 95% CI 2.43–30.80). This model had satisfactory fit and discrimination (goodness-of-fit, $p = 0.72$; area under the curve = 0.83). Notably, the presence of an ACIP condition was not associated with severe disease, even when forced into the multivariate model.

Table 2

Clinical symptoms on admission of 132 children with community-acquired, laboratory-confirmed seasonal influenza

| Clinical symptom | n (%) |
|------------------------|------------|
| Fever/history of fever | 126 (95.5) |
| Cough | 120 (90.9) |
| Coryza/rhinitis | 99 (75) |
| Vomiting | 45 (34.1) |
| Sore throat | 27 (20.5) |
| Diarrhea | 21 (15.9) |
| Seizures | 15 (11.4) |
| Rash | 12 (9.1) |
| Stridor | 5 (3.8) |

3.4. Seasonality

Between 1982 and 2007, there were 364 laboratory-confirmed influenza cases detected from 12 216 clinical specimens (Fig. 1). As a proportion of clinical specimens tested, the monthly rate of

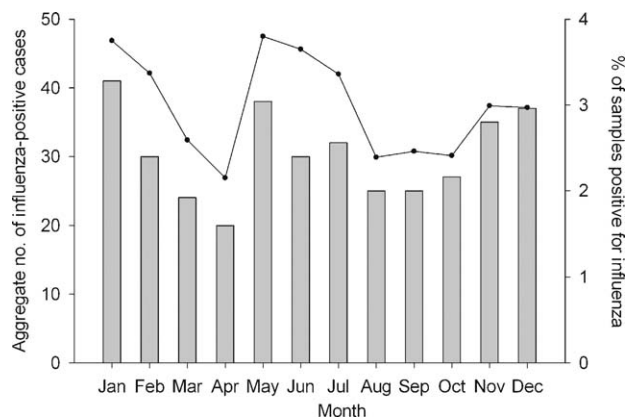


Fig. 1. Seasonal pattern of laboratory-confirmed influenza cases diagnosed in 1982–2007, presented as absolute numbers (bars), and as a percentage of total samples tested (line).

confirmed influenza cases ranged from 2.1% to 3.8% (mean 3.0%). There was year-round influenza activity, with peaks in November–January and May–July.

4. Discussion

We found that influenza had considerable clinical impact on admitted children with and without pre-existing medical conditions. As seen in previous studies,^{3–6,8,13,14} most of the total admissions (84/132 children (63.6%)), children with severe disease (9/16 children (56.3%)), and PICU admissions (8/12 children (66.7%)) were previously healthy, and a majority (87.9%) were <5 years old. The PICU admission rate (9.1%) and disease severity were comparable to those found in other countries.^{3–6,8,13,14} The mean length of inpatient stay was 6.2 days, suggesting considerable socioeconomic losses in terms of school and work days lost. There were three deaths (2.3%) in this study, although influenza-related deaths are rare in children, at 0.2–0.3 per 100 000 person-years in those aged <4 years.¹⁵ Our rate is based on a biased sample of hospitalized patients. However, the number of children with influenza is likely to be underestimated in this study due to the relative insensitivity of diagnosis by immunofluorescence and virus isolation when compared to PCR. Furthermore, almost half of reported influenza-associated deaths may occur in the emergency department or at home, and not in an inpatient setting.¹⁶ Therefore, there is a critical need for further study of the true influenza burden in Malaysia.

In this study, severe influenza was associated with age <12 months (25.6% of this age group had severe disease), female sex, and the absence of rhinitis at presentation. The latter association has been reported previously,⁴ and these symptoms may indicate an upper respiratory tract infection rather than potentially serious involvement of other organs. Underlying medical conditions are known to predispose to severe disease,^{7,13} but we did not find this in our patients, in agreement with another study.⁴ This may be due to the small sample size, or because healthy children with mild influenza may be less likely to be brought to hospital than children with medical conditions. In support of this, hospitalized children with ACIP conditions had significantly shorter duration of symptoms, suggesting they had sought medical attention earlier.

The incidence and overall burden of influenza in Malaysia is not known, as surveillance data are limited. In a previous hospital-based study, influenza caused 6.2% of respiratory virus infections, ranking third behind RSV and parainfluenza.¹⁷ We were unable to calculate the incidence rate of influenza hospitalization, as the catchment population served by our hospital is not clearly defined. However, laboratory-confirmed influenza accounted for 0.3% of all pediatric admissions to our hospital. This is comparable to a recent study estimating that RSV infection, widely recognized as a cause of substantial morbidity, causes one in 334 (0.3%) hospitalizations of children <5 years in the USA.¹⁸

Despite the growing evidence that influenza is a significant health problem in developing countries, the usage of influenza vaccine is extremely low.¹⁹ In Malaysia, there are no recommendations for influenza vaccination in children, and the unknown burden of influenza precludes cost–benefit analysis. If Malaysia followed the 2006 ACIP recommendations for vaccinating all children aged 6–59 months and those with high-risk conditions, and taking the lower limit of reported vaccine efficacy of 54–91%,⁷ up to 57 of the 131 hospitalizations in this study may have been prevented. In practice, however, influenza vaccine uptake is low, even in developed countries with adequate resources. In the USA, of 90 cases of influenza-associated death in 2004–2007 with indications for vaccination, only 21% had been vaccinated.¹⁶

An indirect benefit of greater use of the seasonal influenza vaccine would be to increase worldwide vaccine production capacity, which is currently insufficient for all countries. This has become critically apparent during the current pandemic, whereby most of the new vaccines will be supplied to developed countries, the main users of seasonal vaccine.²⁰

The few available studies of seasonality suggest that in the tropics, influenza occurs throughout the year, and peaks of activity may occur more than once and last longer than in temperate countries.²¹ Our findings support this and the limited Malaysian data currently available, a national survey of 466 influenza cases from 1997 to 2005.²² Within Southeast Asia, the Malaysian influenza seasonal pattern of year-round activity with biannual peaks (May–July, November–January) is most similar to neighboring Singapore¹⁰ and Vietnam,²³ rather than the year-round activity with single peaks seen in Indonesia (October–January)²⁴ and Thailand (June–September).²⁵ As there are seasonal differences within the region, influenza vaccination programs need to be tailored to individual countries.

In conclusion, community-acquired seasonal influenza has an important impact on children hospitalized in tropical Malaysia. Over a 25-year period, influenza was seen year-round, with biannual peaks. However, detailed knowledge of the epidemiology of influenza is lacking in Malaysia, and the burden of disease is underappreciated. Influenza vaccine is not widely used, but may benefit Malaysian children. To further understand influenza disease in Malaysia, particularly if routine vaccination is considered, comprehensive, prospectively-collected surveillance data are required.

Conflict of interest

No conflict of interest to declare.

Ethical Approval

Ethical approval was obtained from the Medical Ethics Committee of the University Malaya Medical Centre, Kuala Lumpur, Malaysia (reference PR10/15/6-2007).

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